Complete Summary

GUIDELINE TITLE

Management of primary biliary cirrhosis.

BIBLIOGRAPHIC SOURCE(S)

Heathcote EJ. Management of primary biliary cirrhosis. The American Association for the Study of Liver Diseases practice guidelines. Hepatology 2000 Apr;31(4):1005-13. [105 references] PubMed

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Primary biliary cirrhosis

GUIDELINE CATEGORY

Diagnosis
Evaluation
Treatment

CLINICAL SPECIALTY

Family Practice
Gastroenterology
Internal Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To aid the practicing physician in diagnosing primary biliary cirrhosis (PBC), establishing the severity of the disease, recognizing the direct complications of primary biliary cirrhosis and its associated disorders, and finally, to advise on the therapies available that will benefit patients from a symptomatic, preventative, and therapeutic standpoint

TARGET POPULATION

Individuals with primary biliary cirrhosis

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Biochemical Tests
    - Alkaline phosphatase (ALP) with confirmation by checking the gamma glutamyl transpeptidase
    - Serum bilirubin
    - Total serum cholesterol
2. Radiologic Assessment of the Bile Ducts
    - Ultrasound
    - Cholangiography
3. Antimitochondrial Antibody (AMA) Testing
    - Immunofluorescence (IF)
    - Enzyme-linked immunosorbent assay and immunoblotting
4. Immunoglobulin fractions
5. Liver biopsy

Treatment

Specific Therapy for Primary Biliary Cirrhosis (PBC)

1. Ursodeoxycholic acid (UDCA) therapy
2. Immunosuppressive therapy (considered, but insufficient data to support recommendation)
3. Liver transplantation

Management of Complications of PBC

1. Treatment of pruritus with cholestyramine, rifampicin, opioid antagonists, ultraviolet light exposure, and plasmapheresis
2. Treatment of Raynaud´s Syndrome including exposure prevention and calcium channel blockers
3. Treatment of sicca syndrome with artifical tears, adequate dental hygiene, antireflux measures, and lubricating jelly or estrogen creams, dependent on symptom manifestation. Refer to the "Major Recommendations" field.

Preventative Treatment

Varices

1. Screening for varices every 3 years with upper endoscopy
2. Standard prophylactic measures if varices are found

Osteoporosis

1. Bone mineral density with dual x-ray absorptiometry
2. Patient education regarding importance of lifestyle changes
3. Vitamin D and calcium supplements
4. Hormone replacement therapy (HRT)
5. Bisphosphonate therapy

Fat Soluble Vitamin Deficiency

1. Vitamin replacement

Thyroid Disease

1. Serum thyroid stimulating hormone measurement

Pregnancy

1. Evaluation for varices and prescribed beta-blocker if found

MAJOR OUTCOMES CONSIDERED

- Sensitivity and specificity of diagnostic tests
- Prevalence of clinical manifestations and complications of primary biliary cirrhosis
- Symptoms and histological features of primary biliary cirrhosis
- Survival rates
- Need for liver transplantation
- Quality of life
- Side effects of medications

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

These definitions for "Quality of Evidence" have been modified by the Practice Guidelines Committee of the American Association for the Study of Liver Diseases from Categories developed by the Infectious Diseases Society of America´s Quality Standards:

Grade I: Evidence from multiple well-designed randomized controlled trials each involving a number of participants to be of sufficient statistical power.

Grade II: Evidence from at least one large well-designed clinical trial with or without randomization, from cohort or case-control analytic studies, or well-designed meta-analysis.

Grade III: Evidence based on clinical experience, descriptive studies, or reports of expert committees.

Grade IV: Not rated

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines were developed under the auspices of, and approved by, the Practice Guidelines Committee of the American Association for the Study of Liver Diseases.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Recommendations are followed by quality of evidence ratings (Grades I-IV) and categories reflecting the evidence to support the use of a recommendation (A-E), which are defined at the end of the "Major Recommendations" field.

Diagnosis of Primary Biliary Cirrhosis (PBC)

1. In patients with otherwise unexplained elevation in alkaline phosphatase (normal bile ducts on ultrasound), serum testing for antimitochondrial antibodies (AMA) is appropriate (III B).
2. The diagnosis of PBC can be made with confidence in a patient with high-titer AMA ($\geq$ 1:40) and a cholestatic pattern of liver biochemistry in the absence of an alternative explanation. A liver biopsy may also be considered (III B).
3. Patients who are AMA positive ($\geq$1:40) with a normal serum alkaline phosphatase, should be followed prospectively with annual reassessment of biochemical testing (III B).
4. In patients with otherwise unexplained elevation in alkaline phosphatase (normal bile ducts on ultrasound) and a negative AMA test, antinuclear antibodies (ANA), smooth muscle antibodies (SMA), and immunoglobulins should be tested and a liver biopsy should be performed (III B).

Specific Therapy for PBC

Ursodeoxycholic Acid Therapy

Appropriately selected patients with PBC with abnormal liver biochemistry should be advised to take ursodeoxycholic acid (UDCA), 13 to 15 mg/kg daily in either divided doses or as a single daily dose. If cholestyramine is used, 4 hours should elapse between cholestyramine intake and UDCA administration (I A, D, E).

Liver Transplantation

Liver transplantation in PBC is recommended for liver failure (II A, C, D). Liver transplantation may be recommended in appropriately selected patients for (1) uncontrollable pruritus (IV C); and (2) severe osteoporosis (IV C).

Management of Complications of PBC

Treatment of pruritus

1. Cholestyramine is the drug of first choice (III C).
2. In patients who fail or are intolerant to the side effects of cholestyramine, rifampicin should be used as a second line therapy (III C).

3. Opioid antagonists can be considered in resistant cases (III C).
4. Liver transplantation is indicated for uncontrollable pruritus (IV).

Management of the Sicca Syndrome

1. All patients should be asked directly about dry eyes, dry mouth, dysphagia, and a dry vagina in women, because patients often do not volunteer these symptoms (III C).
2. If symptoms are present, appropriate therapy should be offered.

Preventative Treatment

Portal Hypertension (Varices)

1. PBC patients should be screened for the presence of varices when first diagnosed and every 3 years until found (III B, C).
2. If and when varices are found, standard prophylactic measures should be taken.

Osteoporosis

1. Bone mineral density should be assessed with dual X-ray absorptiometry when the diagnosis of PBC is first made and every 2 years thereafter.
2. Education regarding the importance of lifestyle changes (e.g., regular exercise, smoking cessation) and vitamin D and calcium supplementation should be given (III C).
3. Hormone replacement therapy (HRT), best via the transdermal route, is recommended where appropriate (III C).
4. If osteoporosis is evident, therapy with a bisphosphonate is advised (III D).

Fat Soluble Vitamin Deficiency

In patients with hyperbilirubinemia, fat soluble vitamin replacement is likely best given using the water soluble form of the fat soluble vitamins (III C).

Thyroid Disease

Serum thyroid stimulating hormone should be checked at diagnosis of PBC and periodically thereafter (III C).

Pregnancy

1. It is currently recommended that any specific therapy (e.g., UDCA) be withheld in women with PBC contemplating pregnancy because its safety during the first trimester has not been proven. UDCA therapy during the last trimester of pregnancy appears to be safe and may be beneficial in mothers with cholestasis (III C, D).
2. Patients who are pregnant should undergo an esophagogastroduodenoscopy to check for varices and given nonselective beta-blocker therapy if varices are found. The obstetrician should be advised to minimize the duration of the second stage of labor (III C).

Definitions

Quality of evidence

Grade I: Evidence from multiple well-designed randomized controlled trials each involving a number of participants to be of sufficient statistical power.

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Grade III: Evidence based on clinical experience, descriptive studies, or reports of expert committees.

Grade IV: Not rated

Evidence to support use

A. Survival benefit
B. Improved diagnosis
C. Improvement in quality of life
D. Relevant pathophysiologic parameters improved
E. Impacts cost of health care

CLINICAL ALGORITHM(S)

Algorithms are provided in the original guideline document for the diagnosis of primary biliary cirrhosis and for the management of complications of primary biliary cirrhosis.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence is specifically stated for each recommendation (see the "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Overall Benefit

Appropriate diagnosis of primary biliary cirrhosis (PBC) and application of treatment for underlying disease and complications of PBC.

Specific Benefits

- The analysis of data collected from 548 patients shows that ursodeoxycholic acid (UDCA) therapy leads to a significant increase in survival after up to 4 years of therapy, as judged by time to liver transplantation.
- UDCA treatment is associated with a marked improvement in serum biochemical markers of cholestasis, i.e., bilirubin, alkaline phosphatase, and gamma glutamyl transpeptidase, including a fall in serum cholesterol levels.
- Treatment with UDCA reduces the rate of development of esophageal varices, but it does not reduce the rate of bleeding from varices.
- The original study with cholestyramine indicated that this anion-binding resin led to marked improvement of the symptoms of pruritus.
- A crossover trial indicated that rifampicin caused good control of pruritus in primary biliary cirrhosis patients at doses of 150 mg 2 times a day or 3 times a day.
- Rifampicin has also been shown to improve the biochemical pattern of patients with primary biliary cirrhosis (when given long term).
- The first study using opioid antagonists for treatment of pruritus used the oral drug nalmephene, which showed an overall benefit when given for up to 9 months, but treatment was associated with the symptoms of narcotic "withdrawal" in some patients. Currently, this drug is not licensed for the treatment for pruritus from cholestasis.
- An excellent crossover study showed that intravenous naloxone led to a significant reduction in pruritus, measured using a highly objective system. However, it is inappropriate for long-term use because it has to be given intravenously. Recently, naltrexone has been assessed in a short-term randomized controlled trial and was reported not to give rise to withdrawal symptoms but to cure pruritus in half of the patients treated. Its use also improved the symptoms of fatigue and depression. Longer and larger studies are needed to fully assess the value of naltrexone in controlling the pruritus of primary biliary cirrhosis in the long term, to assess whether tolerance develops, and to provide a more complete understanding of its side effects.

Subgroups Most Likely to Benefit:

The greatest benefit from ursodeoxycholic acid (UDCA) therapy is seen in those with the most severe disease, because predictably, more events were observed in patients with severe rather than with mild disease.

POTENTIAL HARMS

- Side effects from ursodeoxycholic acid (UDCA) therapy use are rare, the most common being diarrhea.
- Many patients find cholestyramine unpleasant to take and constipating, and they often request other therapy.
- Side effects of rifampicin include unconjugated hyperbilirubinemia, dark staining urine, and on occasion, hepatitis, thrombocytopenia, and sometimes renal tubular damage.
- Nalmephene has been associated with the symptoms of narcotic "withdrawal" in some patients.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

These guidelines were developed under the auspices of, and approved by, the Practice Guidelines Committee of the American Association for the Study of Liver Diseases. They are intended to suggest preferable approaches to the clinical management of liver diseases. They are flexible and are not intended as the only acceptable approach to treatment. As the appropriate level of skill or course of treatment will vary in light of the relevant facts and circumstances surrounding each individual case, these guidelines are not intended to define the applicable standard of medical care and may be updated periodically as new information becomes available.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Heathcote EJ. Management of primary biliary cirrhosis. The American Association for the Study of Liver Diseases practice guidelines. Hepatology 2000 Apr;31(4):1005-13. [105 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2000 Apr

GUIDELINE DEVELOPER(S)

American Association for the Study of Liver Diseases - Private Nonprofit Research Organization

SOURCE(S) OF FUNDING

American Association for the Study of Liver Diseases

GUIDELINE COMMITTEE

Practice Guidelines Committee

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American Association for the Study of Liver Diseases Web site.

Print copies: Available from the American Association for the Study of Liver Diseases, 1729 King Street, Suite 200; Alexandria, VA 22314; Phone: 703-299-9766; Web site: www.aasld.org; e-mail: aasld@aasld.org.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on May 9, 2003. The information was verified by the guideline developer as of June 12, 2003.

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